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(54) Title: **FEXOFENADINE POLYMORPH**

(57) Abstract: The present invention provides a novel fexofenadine hydrochloride polymorph. The polymorph is particularly useful as a medicament for use as an antihistamine, antiallergy agent or bronchodilator.

FEXOFENADINE POLYMORPH**FIELD OF THE INVENTION**

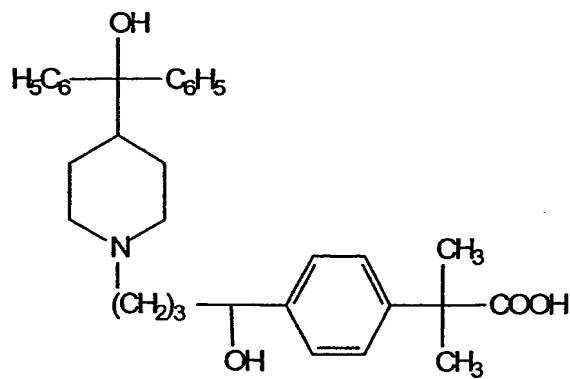
This application relates to a new polymorph of fexofenadine and to a process for the preparation thereof.

5 BACKGROUND OF THE INVENTION

Terfenadine, 1-(p-tert-butylphenyl)-4-[4'-(alpha-hydroxydiphenylmethyl)-1'-piperidenyl]-butanol, is a non-sedating anti-histamine. It is known to be a specific H₂-receptor antagonist that is also devoid of any anticholingeric, antiserotonergic and antiadrenergic effects both *in vivo* and *in vitro*.

10 However, terfenadine has been linked to potentially fatal abnormal heart rhythms in some patients with liver disease or who also take the antifungal drug ketoconazole or the antibiotic erythromycin.

In animal and human metabolic studies, terfenadine was shown to undergo high first-pass effect, which results in readily measurable plasma concentrations of the major metabolite 15 4-[4-(hydroxy diphenyl methyl)-1-piperidenyl]-1-hydroxy butyl]- α,α -dimethylphenyl acetic acid, also known as terfenadine carboxylic acid metabolite or fexofenadine, the structure of which is illustrated below.



Fexofenadine possesses anti-histamine activity in animal models and is believed to lack the cardiac side effects seen with terfenadine. Moreover, it has been postulated that terfenadine is in fact a pro-drug and fexofenadine is the active agent.

There has therefore been considerable interest in preparing fexofenadine since its use may 5 eliminate a number of the side effects associated with the use of terfenadine.

Fexofenadine hydrochloride is an effective antihistamine which avoids adverse effects associated with the administration of terfenadine.

The pharmaceutical industry has, of late, conducted studies on polymorphism in drugs and the difference in the activity of different polymorphic forms of a given drug. The term

10 polymorphism is meant to include different physical forms, crystal forms, crystalline/liquid crystalline/non-crystalline (amorphism) forms. Polymorphism has interested scientists after observations were made that many antibiotics, antibacterials, tranquillisers, etc. exhibit polymorphism and some/one of the polymorphic forms of a given drug exhibits superior bioavailability and consequently shows much higher activity compared to other 15 polymorphs. It has also been disclosed that some amorphic forms of a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline form. For some therapeutic indications one bioavailability pattern may be favoured over another.

Polymorphic forms of fexofenadine have been identified in the prior art. In WO 00/71124

20 there is described an amorphic form of fexofenadine hydrochloride prepared by dissolving crystalline fexofenadine hydrochloride in a suitable solvent or dissolving fexofenadine base in a suitable solvent and adding a suitable solvent containing hydrogen chloride and recovering the amorphic form of fexofenadine hydrochloride from the solution thereof by spray drying or freeze drying techniques.

25 WO 95/31437 also describes polymorphic forms of fexofenadine, in particular so-called anhydro form I and form III of fexofenadine hydrochloride and hydrated forms II and IV of fexofenadine hydrochloride. The Form I polymorph is perhaps the closest in structure to the polymorph of the present invention, nevertheless, the Form I polymorph exhibits a very different X-ray diffraction spectrum than that required below.

30 DESCRIPTION OF THE INVENTION

The present inventors have surprisingly found a new polymorphic form of fexofenadine hydrochloride which may be isolated using pentanone. It is envisaged that the polymorphic

form of fexofenadine hydrochloride described herein will have particularly beneficial medicinal properties, be especially bioavailable and have a long shelf life.

Thus, the invention provides a fexofenadine hydrochloride polymorph having the following X-ray powder diffraction pattern obtained using $K_{\alpha}1$ Cu($\lambda=1.5406\text{\AA}$) radiation

D-space, Angstroms
12.25
11.28
8.78
8.17
7.73
6.77
6.32
6.11
5.61
5.32
5.13
4.98
4.88
4.85
4.32
3.87
3.64
3.49
3.38
3.23
2.91
2.80

The invention also provides a pharmaceutical composition comprising a fexofenadine hydrochloride polymorph as hereinbefore described along with one or more pharmaceutical carriers/excipients.

The invention further provides a fexofenadine hydrochloride polymorph as hereinbefore

5 described for use in medicine, e.g. as a antihistamine, antiallergy agent or bronchodilator.

The invention still further provides the use of a fexofenadine hydrochloride polymorph as hereinbefore described in the manufacture of an medicament for use as an antihistamine, antiallergy agent or bronchodilator.

The water content (measured by the Karl Fischer water determination method) of the

10 fexofenadine hydrochloride polymorph of the invention should be below 0.5%, e.g. between 0.1 to 0.4%, preferably below 0.3% e.g. 0.2 to 0.3%.

The melting point of the fexofenadine hydrochloride polymorph (as measured by differential scanning calorimetry) should be in the range: melt endotherm onset 195 to 197°C.

15 The infrared spectrum of the fexofenadine hydrochloride polymorph has also been obtained and is described below. The underlined peaks are considered the most characteristics of the polymorph.

IR $\nu_{\text{max}}(\text{cm}^{-1})$ (KBr): 3412, 3051, 2980, 2940, 2871, 2725, 1713, 1512, 1492, 1468, 1447,

1389, 1273, 1250, 1238, 1169, 1150, 1099, 1091, 1066, 1020, 1009, 1000, 967, 881,

20 841, 819, 751, 744, 704, 693, 664, 637.

Thus, the invention also provides a fexofenadine polymorph having the characteristic IR peaks described above.

The X-ray diffraction pattern of the polymorph may have the following peaks. (Intensities may vary due to preferred orientation).

D-space, Angstroms	Intensity, I/I ₀ , %
12.25	43
11.28	28
8.78	60
8.17	61
7.73	81
7.43	28
6.77	77
6.32	94
6.11	46
5.61	34
5.32	30
5.13	92
4.98	100
4.88	65
4.85	69
4.71	38
4.63	42
4.55	49
4.39	57
4.32	45
4.14	49
4.03	38
3.97	41
3.87	90
3.69	31
3.64	72
3.49	87

D-space, Angstroms	Intensity, I/I ₀ , %
3.46	37
3.38	39
3.36	33
3.23	38
3.16	26
3.13	31
2.98	24
2.95	27
2.91	37
2.87	20
2.84	22
2.80	25
2.79	23
2.57	19
2.34	20
2.19	20

The fexofenadine hydrochloride polymorph of the invention may be obtained by suspending 4-[4[4-(hydroxy diphenyl methyl)-1-piperidenyl]-1-hydroxy butyl]- α,α -dimethylphenyl acetic acid (fexofenadine) in pentanone. The suspension is concentrated

5 whilst maintaining the Karl Fischer of the suspension below 1%, allowed to cool and HCl added in alcohol. On acid addition, a precipitate forms and after further cooling, this is collected by filtration, washed and dried. The resulting solid is resuspended in pentanone, the suspension refluxed and the polymorph of the invention isolated by filtration upon cooling.

10 Thus, the invention further provides a process for the preparation of a fexofenadine hydrochloride polymorph comprising:

- I) mixing fexofenadine in pentanone to form a suspension;
- II) heating said suspension so that an amount of pentanone is distilled off whilst maintaining the Karl Fischer of the suspension below 1% to form a slurry;
- III) contacting said slurry with HCl in alcohol; and
- 5 IV) isolating the resulting precipitate and refluxing the same in pentanone.

The invention thus further provides a fexofenadine hydrochloride polymorph obtainable by, e.g. obtained by, a process as hereinbefore described.

The pentanone employed in the process of the invention should preferably be 3-pantanone. It is believed however, that other solvents such as 2-pantanone, and other 10 ketones may also be employed. Typically, approximately 10 ml of pentanone per 1 g of fexofenadine should be initially mixed.

During the distillation step (II), it is preferred if at least 20%, e.g. at least 25%, such as approximately 30%, of the pentanone is distilled off to leave the slurry. Throughout this process the Karl Fischer of the suspension must be maintained below 1%, preferably below 15 0.5%, especially below 0.3%.

"Karl Fischer" refers to a conventional method for determining the content of water in solids and organic solvents. Thus, "Karl Fischer" is a measure of the water content of the suspension and is measured using standard means, see, e.g., the Skoog and West, "Fundamentals of Analytical Chemistry", 4th ed., 1982, pages 389-91, (ISBN 4-8337-20 0082-4).

The hydrochloric acid added to the slurry in step III is mixed with an alcohol. Preferably, the ratio of acid to alcohol should be in the range 1:1 to 1:2, especially around 2:3. It is also preferable to use a 2-3M solution of hydrochloric acid in alcohol. The alcohol of use is preferably ethanol although other alcohols such as propanol, methanol or isopropanol 25 could be used. A slight molar excess of HCl (e.g. around 1.05:1 or 1.1:1) should be used in proportion to fexofenadine. Moreover, it is preferred if as little HCl/alcohol solution is used as possible since larger volumes of the acid/alcohol solution impedes precipitation. Hence, a more concentrated solution is preferred since less solution is required in order for the HCl to be in slight molar excess.

30 After addition of the acid precipitation occurs. It is believed that this is a fexofenadine hydrochloride pentanone solvate. The acidified mixture may be stirred to ensure full

precipitation after which the mixture may be cooled to approximately 0°C. The precipitate may then be isolated by conventional techniques, e.g. filtration.

Conversion through to the polymorph of the invention is achieved by refluxing the precipitate (fexofenadine hydrochloride pentanone solvate) in pentanone, typically for 1 to 5 3, e.g. about 2 hours. On cooling the desired polymorph may be isolated by conventional techniques, e.g. filtration.

The fexofenadine polymorph described above may be formulated and employed in medical treatment as is well-known in the art. For example, fexofenadine may be employed as an antihistamine, antiallergy agent or bronchodilator and may be administered alone or in 10 conjunction with other active agents. Pharmaceutical preparations of fexofenadine or its derivatives may take the form of tablets, capsules, powders, solutions, suspensions or emulsions, etc. These may be prepared using conventional pharmaceutical excipients or carriers.

The polymorph of the invention may be administered along with other polymorphs of 15 fexofenadine or fexofenadine hydrochloride and the pharmaceutical composition of the invention covers this possibility. Thus, for example, the pharmaceutical composition of the invention may comprise 10%, preferably at least 20%, especially at least 30% of the fexofenadine polymorph of the invention.

Fexofenadine or its derivatives may be administered orally, parenterally, or across a 20 mucous membrane. The skilled artisan is aware of other administration methods.

The amount of fexofenadine or its derivatives employed will vary depending on the nature of the patient but will be readily determined by the person skilled in the art.

The invention will now be further described with reference to the following non-limiting examples and Figures.

25 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the DSC curve of the fexofenadine hydrochloride polymorph of the invention showing a melt endotherm onset of 196.56°C.

Figures 2a to 2c depict the IR spectrum of the fexofenadine hydrochloride polymorph of the invention.

30 Figure 3 depicts the X-ray diffraction pattern of the fexofenadine hydrochloride polymorph of the invention.

EXAMPLES**Example 1**

4-[4[4-(hydroxy diphenyl methyl)-1-piperidinyl]-1-hydroxy butyl]- α,α -dimethylphenyl acetic acid (330.0 g, 0.598 mol) was stirred with 3-pentanone (3000 ml). The resulting suspension was heated to distill off 900 ml of the 3-pentanone whilst maintaining the Karl Fischer of the suspension below 1%. The Karl Fischer of the suspension was initially 0.28%, after distillation, the Karl Fischer of the slurry was 0.13%. If the Karl Fischer is greater than 1% then more 3-pentanone should be added and distillation restarted.

The resulting thick slurry was cooled and subsequently treated with a 2.7 N solution of hydrochloric acid in ethanol (250 ml, 0.675 mol). The reaction was stirred and a precipitate observed. The solution was cooled to 0°C and stirred for one hour. The solid was collected by filtration on a sintered glass funnel, washed with 3-pentanone (450 ml) and vacuum dried at 40 to 50°C.

A suspension of this solid (328.8 g, Loss On Drying approx 10%) was heated at reflux with 3-pentanone (3619 ml). Complete conversion into the fexofenadine hydrochloride polymorph was checked by IR. The suspension was cooled to 0°C and stirred for 1 hour. The solid was collected by filtration on a sintered glass funnel, washed with 3-pentanone (329 ml) and vacuum dried at 40 to 50°C.

Yield 282 g of fexofenadine hydrochloride polymorph.

20 Analytical data:

The solvent content, measured by gas chromatography was approximately 0.3% (3-pentanone).

Melting point was determined using DSC (Mettler Toledo STAR^e System, DSC821^emodule). The temperature was taken from 40°C to 240°C, 5°C/min. Melt endotherm onset 195-25 197°C. (See Figure 1)

IR was measured using a Nicolet AVATAR 320. The results are presented in Figures 2a-c.

The X-ray powder diffraction pattern of the product was measured using a Debye-Scherrer INEL CPS-120, radiation K_α1 Cu(λ =1.5406Å). The results are presented below and in Figure 3.

-N-	2 theta	---d---	---Cps---	---%
1	7.211	12.2491	0.50	43.36
2	7.828	11.2842	0.32	28.47
3	10.062	8.7833	0.69	60.46
4	10.814	8.1745	0.69	60.66
5	11.435	7.7316	0.92	80.51
6	11.895	7.4338	0.32	27.98
7	13.057	6.7749	0.88	77.06
8	13.995	6.3228	1.08	94.45
9	14.485	6.1098	0.52	45.50
10	15.358	5.7646	0.26	22.48
11	15.793	5.6068	0.39	34.33
12	16.108	5.4977	0.28	24.96
13	16.651	5.3198	0.34	30.19
14	17.284	5.1264	1.05	91.63
15	17.803	4.9782	1.14	100.00
16	18.168	4.8788	0.75	65.40
17	18.446	4.8060	0.79	68.98
18	18.842	4.7057	0.43	37.66
19	19.171	4.6258	0.48	41.97
20	19.489	4.5509	0.56	49.42
21	20.228	4.3863	0.65	56.67
22	20.533	4.3218	0.51	44.67
23	21.210	4.1855	0.32	28.44
24	21.439	4.1412	0.56	48.76
25	22.053	4.0273	0.43	38.05
26	22.354	3.9738	0.47	40.78
27	22.938	3.8739	1.03	89.88
28	24.114	3.6876	0.35	30.58
29	24.404	3.6444	0.83	72.41
30	24.712	3.5997	0.27	24.01
31	25.516	3.4881	1.00	87.42
32	25.737	3.4586	0.43	37.30
33	26.345	3.3802	0.44	38.83
34	26.546	3.3550	0.38	33.31
35	27.586	3.2309	0.43	37.64
36	28.018	3.1820	0.29	25.62
37	28.256	3.1557	0.30	26.28
38	28.512	3.1280	0.36	31.34
39	28.658	3.1124	0.26	22.87
40	29.227	3.0530	0.29	25.26
41	30.010	2.9751	0.28	24.16
42	30.312	2.9462	0.30	26.69
43	30.664	2.9131	0.42	36.59

44	31.103	2.8730	0.23	20.07
45	31.428	2.8441	0.25	21.97
46	31.887	2.8042	0.29	25.04
47	32.085	2.7873	0.26	22.68
48	33.527	2.6707	0.27	23.26
49	33.808	2.6491	0.23	20.05
50	34.637	2.5876	0.19	16.67
51	34.946	2.5654	0.22	19.32
52	35.350	2.5370	0.18	16.18
53	35.680	2.5143	0.18	15.43
54	36.007	2.4922	0.20	17.20
55	36.327	2.4710	0.17	14.70
56	36.965	2.4298	0.16	14.09
57	37.286	2.4096	0.19	16.64
58	37.932	2.3700	0.21	18.18
59	38.523	2.3350	0.22	19.68
60	38.680	2.3259	0.21	17.98
61	38.897	2.3134	0.21	18.44
62	39.911	2.2570	0.16	13.89
63	41.190	2.1898	0.23	20.12
64	41.594	2.1695	0.14	11.97
65	42.111	2.1440	0.13	11.78
66	42.649	2.1182	0.15	12.87
67	42.981	2.1026	0.16	14.23
68	43.289	2.0884	0.14	12.24
69	43.635	2.0726	0.14	12.19
70	44.117	2.0510	0.15	13.50
71	44.500	2.0343	0.17	14.94
72	45.025	2.0118	0.13	10.97
73	45.377	1.9970	0.12	10.27
74	45.750	1.9816	0.14	12.41
75	46.241	1.9617	0.12	10.27
76	46.683	1.9441	0.12	10.51
77	46.903	1.9355	0.13	11.09
78	47.657	1.9066	0.11	9.81
79	48.356	1.8807	0.12	10.07
80	48.900	1.8611	0.12	10.66
81	49.154	1.8520	0.12	10.92
82	49.703	1.8328	0.11	9.54
83	50.150	1.8175	0.15	12.87

CLAIMS

1. A fexofenadine hydrochloride polymorph having the following X-ray powder diffraction pattern obtained using $K_{\alpha}1$ Cu($\lambda=1.5406\text{\AA}$) radiation

D-space, Angstroms
12.25
11.28
8.78
8.17
7.73
6.77
6.32
6.11
5.61
5.32
5.13
4.98
4.88
4.85
4.32
3.87
3.64
3.49
3.38
3.23
2.91
2.80

2. A fexofenadine polymorph having the characteristic IR peaks IR $\nu_{\text{max}}(\text{cm}^{-1})$ (KBr): 3412, 1713, 1250, 1238, 1150, 1091, 751, 744, 704, 693.
- 5 3. A pharmaceutical composition comprising the fexofenadine hydrochloride polymorph as claimed in claim 1 or 2 along with one or more pharmaceutical carriers/excipients.
4. A fexofenadine hydrochloride polymorph as claimed in claim 1 or 2 for use in medicine.
- 10 5. The use of the fexofenadine hydrochloride polymorph as claimed in claim 1 or 2 in the manufacture of an medicament for use as an antihistamine, antiallergy agent or bronchodilator.
6. A process for the preparation of a fexofenadine hydrochloride polymorph comprising:
 - 15 I) mixing fexofenadine in pentanone to form a suspension;
 - II) heating said suspension so that an amount of pentanone is distilled off whilst maintaining the Karl Fischer of the suspension below 1% to form a slurry;
 - III) contacting said slurry with HCl in alcohol; and
 - IV) isolating the resulting precipitate and refluxing the same in pentanone.
- 20 7. A fexofenadine hydrochloride polymorph obtainable by a process as claimed in claim 6.

AMENDED CLAIMS

[received by the International Bureau on 20 December 2002 (20.12.02);
original claim 2 amended;
remaining claims unchanged (1 page)]

2. A fexofenadine hydrochloride polymorph having the characteristic IR peaks IR $\nu_{\text{max}}(\text{cm}^{-1})$ (KBr): 3412, 1713, 1250, 1238, 1150, 1091, 751, 744, 704, 693.
- 5 3. A pharmaceutical composition comprising the fexofenadine hydrochloride polymorph as claimed in claim 1 or 2 along with one or more pharmaceutical carriers/excipients.
4. A fexofenadine hydrochloride polymorph as claimed in claim 1 or 2 for use in medicine.
- 10 5. The use of the fexofenadine hydrochloride polymorph as claimed in claim 1 or 2 in the manufacture of an medicament for use as an antihistamine, antiallergy agent or bronchodilator.
6. A process for the preparation of a fexofenadine hydrochloride polymorph comprising:
 - 15 I) mixing fexofenadine in pentanone to form a suspension;
 - II) heating said suspension so that an amount of pentanone is distilled off whilst maintaining the Karl Fischer of the suspension below 1% to form a slurry;
 - III) contacting said slurry with HCl in alcohol; and
 - IV) isolating the resulting precipitate and refluxing the same in pentanone.
- 20 7. A fexofenadine hydrochloride polymorph obtainable by a process as claimed in claim 6.

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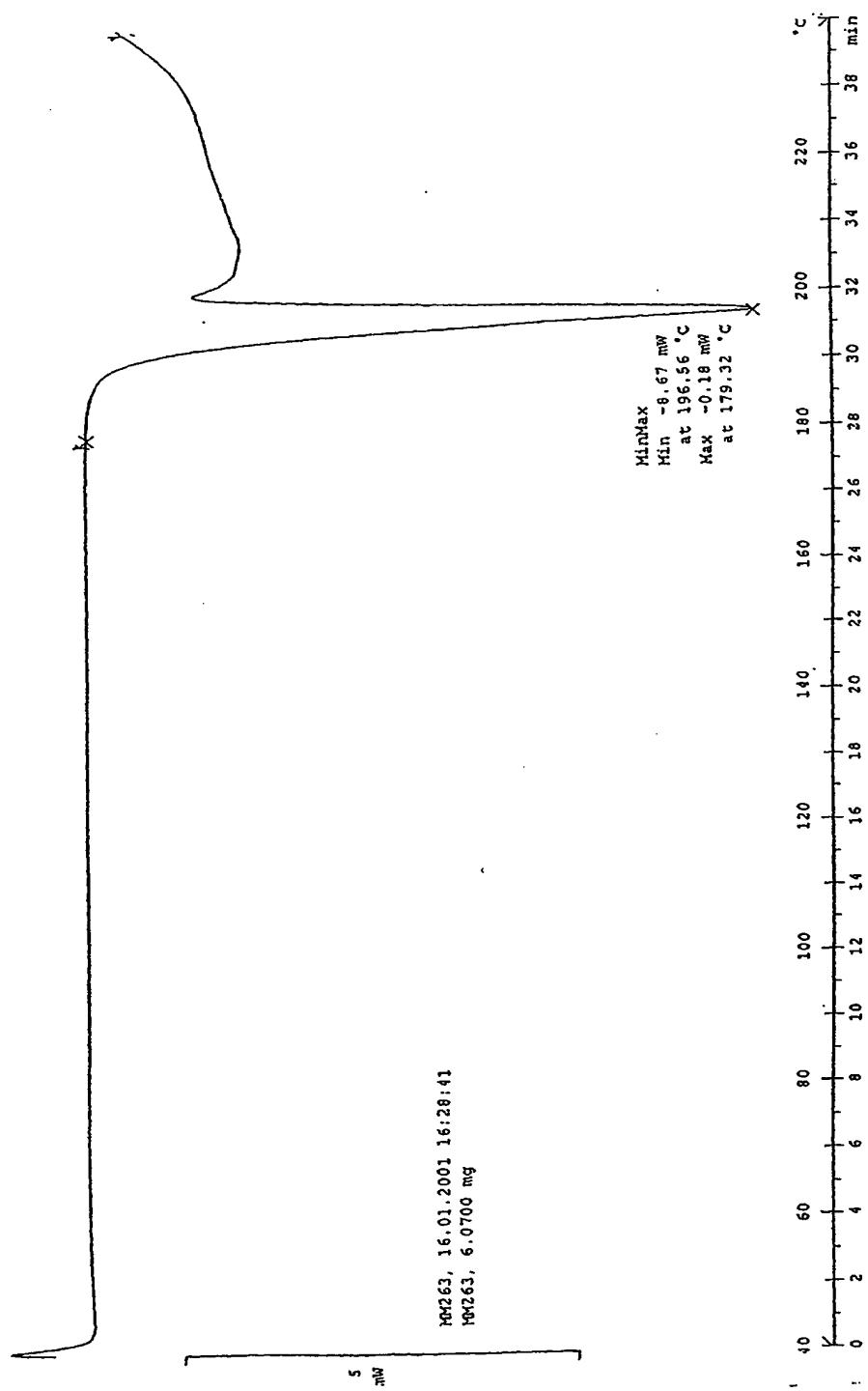


Fig. 1

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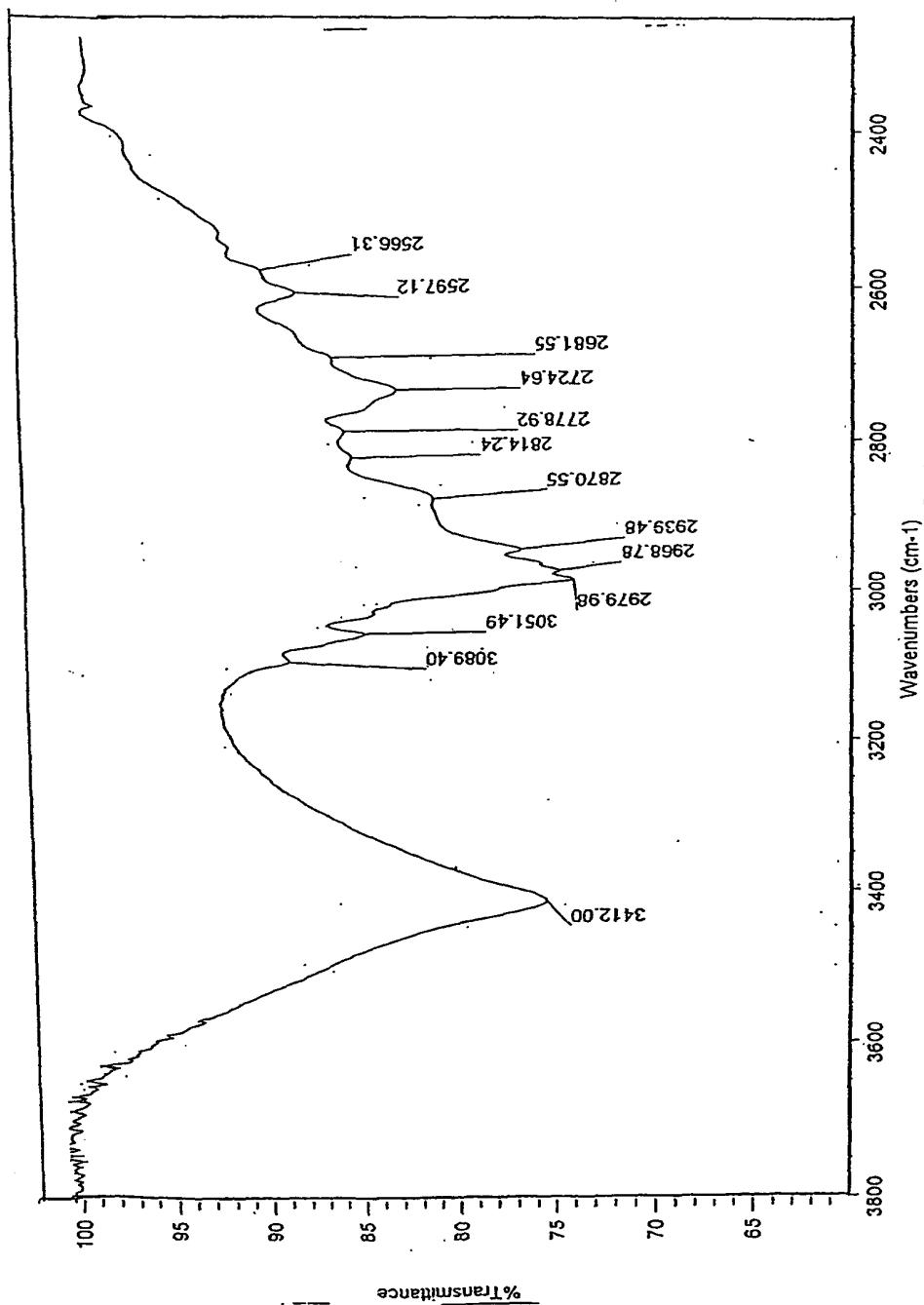


Fig. 2 a

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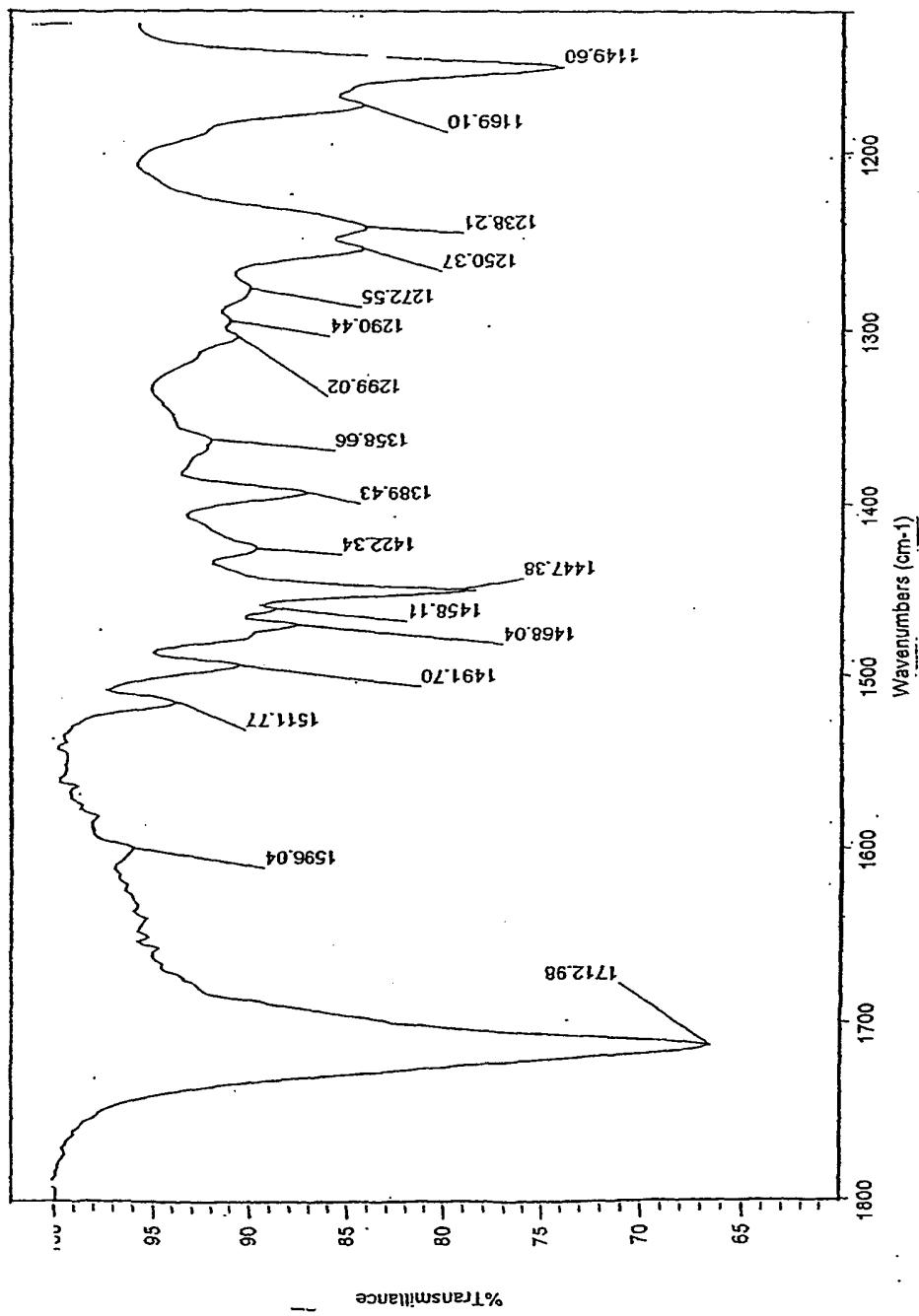


Fig. 2 b

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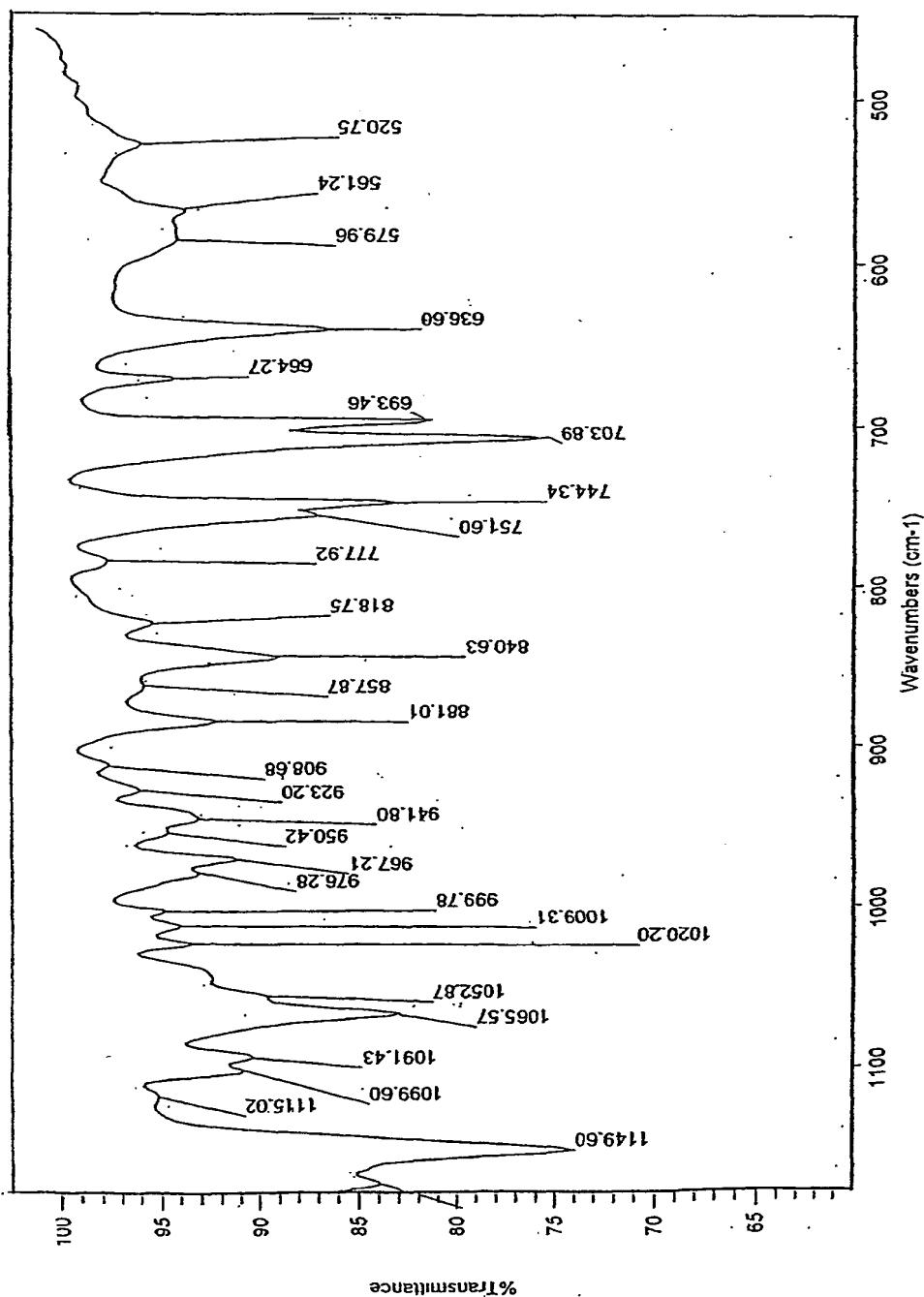


Fig. 2 C

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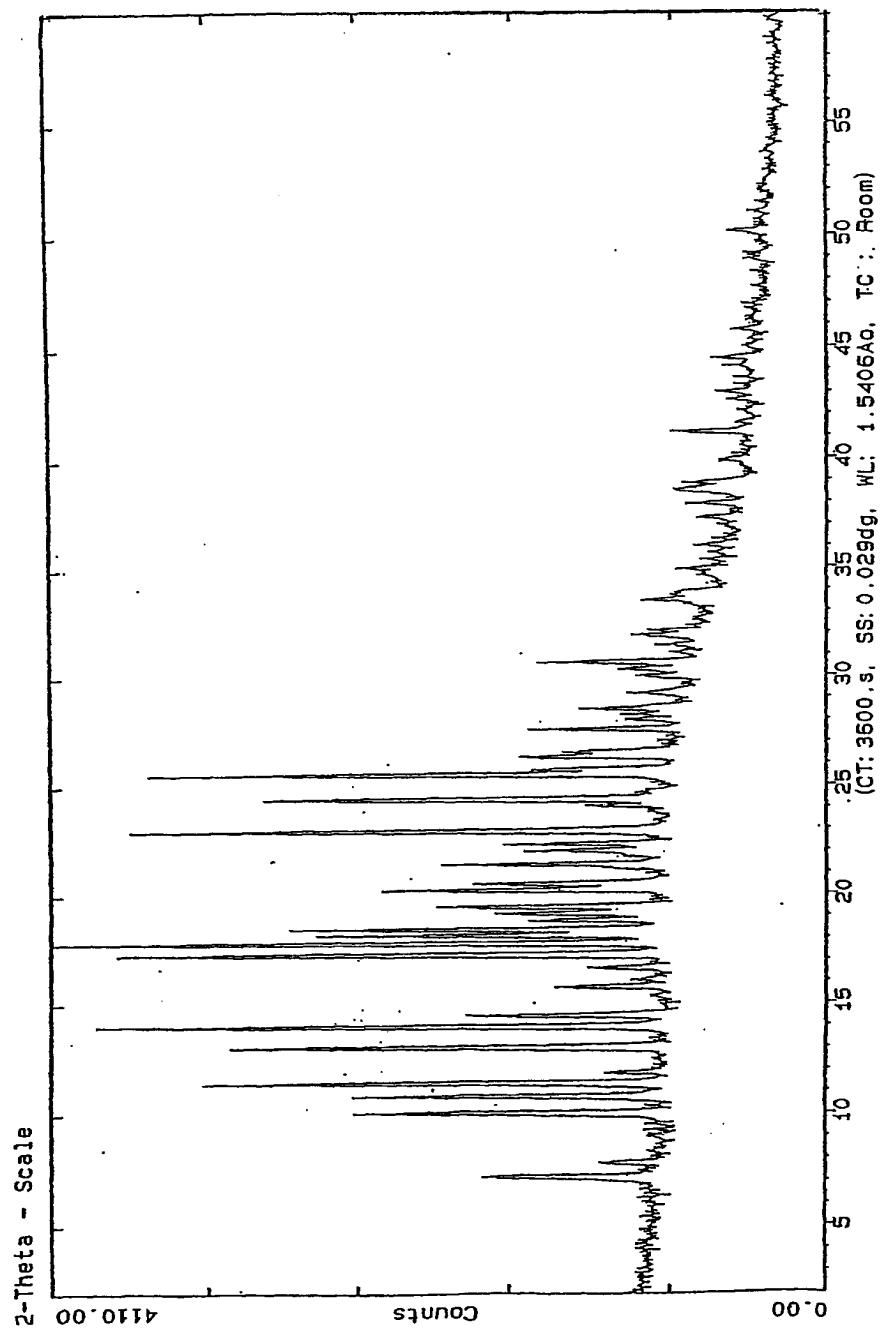


Fig. 3

INTERNATIONAL SEARCH REPORT

Internal	Application No
PCT/IB 02/02954	

A. CLASSIFICATION OF SUBJECT MATTER			
IPC 7	A61K31/445	A61P37/08	C07D211/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
--

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT
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Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 31437 A (MARION MERRELL DOW INC) 23 November 1995 (1995-11-23) cited in the application page 4, line 30 - line 37	1-7

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- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 October 2002	31/10/2002
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax (+31-70) 340-3016	Johnson, C

INTERNATIONAL SEARCH REPORT

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onal application No.
PCT/IB 02/02954

B x 1 Observations wh re certain claims wer 1 und unsearchabl (Continuation of Item 1 first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 2 (part) because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 2 (part)

Claim 2 is formulated as an independent claim and relates to a fexofenadine polymorph, rather than a fexofenadine hydrochloride polymorph. However, claims 3-5 all refer back to the fexofenadine hydrochloride polymorph of claims 1 or 2. Furthermore, in the description the IR peaks defined in claim 2 are attributed to the fexofenadine hydrochloride polymorph having the X-ray diffraction pattern defined in claim 1. There is thus confusion as to whether claim 2 actually relates to the free base or the hydrochloride salt and claim 2 does not fulfil the requirements of Article 6 PCT. As there is no information in the description concerning a preparation of a free base polymorph, and as the free base polymorph would not, in any case, be unitary with the hydrochloride polymorph, claim 2 has only been searched insofar as it relates to the hydrochloride polymorph of claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT
.....nation on patent family members

Intern. Application No
PCT/IB 02/02954

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